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Stroke

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Thrombolysis for Ischemic Stroke Beyond the 4.5-Hour Window: A Meta-Analysis of Randomized Clinical Trials

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BACKGROUND: A minority of patients with stroke qualify for intravenous thrombolysis (IVT) within 4.5-hour window. The safety and efficacy of IVT beyond this period have not been well studied.

METHODS: We systematically searched MEDLINE, Embase, Cochrane, and ClinicalTrials.gov for relevant randomized clinical trials. Randomized clinical trials comparing IVT versus standard medical care in patients with ischemic stroke beyond 4.5 hours of symptom onset or last known well without mechanical thrombectomy (MT) were included. Primary outcomes were excellent (modified Rankin Scale score of 0–1) and good (modified Rankin Scale score of 0–2) functional outcomes at 90 days, symptomatic intracerebral hemorrhage (sICH), and death at 90 days. Pooled odds ratios (ORs) with 95% CIs were calculated using a random-effects model. Heterogeneity was assessed by Q test and quantified by I^2 values.

RESULTS: Eight randomized clinical trials (1742 patients; mean age, 69.8±9 years, 63.5% men) were included. Compared with standard medical care, IVT achieved higher rates of excellent (OR, 1.43 [95% CI, 1.17–1.75]; Q=2.30; P=0.94; I^2=0%) and good functional outcomes (OR, 1.36 [95% CI, 1.12–1.66]; Q=2.07; P=0.96; I^2=0%) at 90 days but also increased sICH rates (OR, 4.25 [95% CI, 1.67–10.84], Q=0.48; P=0.99; I^2=0%). Mortality at 90 days did not significantly differ between treatment groups (OR, 1.28 [95% CI, 0.87–1.89]; Q=4.63; P=0.59; I^2=0%). Subanalyses yielded numerically higher odds of excellent functional outcomes when patients were selected with perfusion imaging (3 studies, OR, 1.45 [95% CI, 1.08–1.94]) compared with diffusion-weighted imaging–fluid-attenuated inversion recovery mismatch (3 studies, OR, 1.34 [95% CI, 0.94–1.91]) and when treated with tenecteplase (3 studies, OR, 1.47 [95% CI, 1.06–2.04]) compared with alteplase (5 studies, OR, 1.38 [95% CI, 1.08–1.78]).

CONCLUSIONS: IVT for ischemic stroke beyond 4.5 hours, without MT, led to increased odds of excellent and good functional outcomes compared with standard medical care, despite higher odds of sICH, and a nonsignificant numerical increase in mortality.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: alteplase ■ clinical trials ■ hemorrhage ■ ischemic stroke ■ tenecteplase ■ thrombectomy ■ thrombolysis

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Intravenous thrombolysis (IVT) is the established treatment for ischemic stroke in eligible patients within 4.5 hours of symptom onset or patient last known well (LKW).[1] However, only a small proportion of patients are eligible and able to receive IVT within this window.[2] Furthermore, there is limited evidence regarding the safety and efficacy of IVT in the extended time window (ie, beyond 4.5 hours). Mechanical thrombectomy (MT)

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Nonstandard Abbreviations and Acronyms

DWI-FLAIR	diffusion-weighted imaging–fluid-attenuated inversion recovery
IVT	intravenous thrombolysis
LKW	last known well
mRS	modified Rankin Scale
MT	mechanical thrombectomy
NBP	DI-3-n-butylphthalide
OR	odds ratio
RCT	randomized clinical trial
sICH	symptomatic intracranial hemorrhage

has revolutionized the treatment of ischemic stroke and is now the primary intervention for patients with large-vessel occlusion. Recent trials have demonstrated its efficacy even in the extended time window.[3] However, in many geographic locations, including developed countries, timely access to MT is not feasible, and it is often unavailable in low- or middle-income countries.[4,5] Consequently, IVT remains the sole option available for a significant portion of the global population suffering from acute ischemic stroke.

Data regarding the safety and efficacy of IVT in the extended time window show conflicting findings. An individual patient-level meta-analysis of 4 trials investigating intravenous alteplase without MT in the extended time window or LKW >4.5 hours with diffusion-weighted imaging–fluid-attenuated inversion recovery (DWI-FLAIR) or perfusion mismatch showed better functional outcomes at 90 days compared with standard medical care.[6] However, the range of IVT is expanding, with tenecteplase and reteplase being investigated for their efficacy and safety in acute ischemic stroke as potential alternatives to alteplase.[7,8] The TRACE-III trial (Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events-III), which included patients with documented large-vessel occlusion, demonstrated that intravenous tenecteplase in the extended time window, without MT, resulted in a higher percentage of patients with better functional outcomes compared with standard medical care.[7] However, the TIMELESS trial (Thrombolysis in Imaging-Eligible, Late-Window Patients to Assess the Efficacy and Safety of Tenecteplase), which also used intravenous tenecteplase in the extended time window for patients with large-vessel occlusion, most of whom underwent subsequent MT, did not show improved functional outcomes, although exposure to the thrombolytic agent before thrombectomy was short (median, 16 minutes).[9]

We performed a systematic literature review and a meta-analysis evaluating the safety and efficacy of IVT for patients suffering from ischemic stroke in the extended time window, without undergoing MT. We aimed to synthesize the existing evidence, address gaps in understanding, and provide comprehensive insights into the safety and efficacy of IVT, which remains the only treatment option for a large worldwide population.

METHODS

The authors declare that all supporting data are available within the article and its Supplemental Material.

This systematic review and meta-analysis followed the guidelines established by the Cochrane Handbook[10] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[11] The protocol for this study was registered in the International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/PROSPERO/; Unique identifier: CRD42024561152).

Eligibility Criteria

The studies selected for this systematic review met the following criteria: (1) they were randomized clinical trials (RCTs) comparing patients with ischemic stroke who received IVT (IVT group) with those who received only standard medical care or placebo (control group) beyond 4.5 hours of symptom onset or LKW and without MT; (2) they reported at least 1 outcome of interest; and (3) they were published in English. The main outcomes of interest included excellent functional outcomes (modified Rankin Scale [mRS] score of 0–1) and good functional outcomes (mRS score of 0–2) at 90 days, mortality at 90 days, and the incidence of symptomatic intracranial hemorrhage.

Search Strategy and Data Extraction

A comprehensive search was conducted in the MEDLINE, Embase, Cochrane Library, and ClinicalTrials.gov databases from their inception until June 22, 2024. A predefined research strategy was formulated according to the Population, Intervention, Comparison, and Outcome model and consisted of the following search terms: ("ischemic stroke" OR stroke) AND (thrombolysis OR fibrinolysis OR "fibrinolytic therapy" OR tenecteplase OR alteplase OR tPA) AND ("beyond 4.5 hours" OR "extended time window" OR "late window" OR "at 4.5 to 24 hours" OR "4.5-24 hours" OR "up to 24 hours" OR "after 4.5 hours"). The database search was complemented with a full forward and backward review of the included trial's references. Two authors independently assessed the studies for data extraction and quality assessment (A.G. and M.V.), and any conflict was resolved by a third author (G.C.). The full search queries and their results are listed in Table S1).

End Points and Definitions

Efficacy Outcomes

The primary efficacy outcomes were: (1) excellent functional outcome, defined as a mRS score of 0 or 1 at 90 days, and (2) good functional outcome, defined as a mRS score of 0 to 2 at 90 days.

Secondary efficacy outcomes were (1) the ordinal distribution of mRS scores at 90 days; (2) recanalization, as defined by trial authors[7,12,13]; (3) reperfusion, as defined by trial authors[7,12,14]; and (4) early neurological improvement according to National Institutes of Health Stroke Scale, defined as a

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decrease of ≥4 points or ≥8 points or a score of ≤1 within 24 and 72 hours.[7,12,15,16]

Safety Outcomes

Primary safety outcomes were (1) symptomatic intracranial hemorrhage (sICH) within 36 hours; and (2) 90-day all-cause mortality.

Secondary safety outcomes were (1) any intracranial hemorrhage; (2) parenchymal hemorrhage type 2 within 36 hours; (3) systemic hemorrhage; (4) 7-day mortality; and (5) 90-day intervention-related mortality.

Some end point definitions varied across the included trials; detailed definitions are available in Tables S2 and S3.

Subanalysis

For the primary safety and efficacy outcomes, we performed subanalyses based on the thrombolytic agent used (alteplase or tenecteplase) and on imaging criteria (DWI-FLAIR mismatch or computed tomography/magnetic resonance imaging perfusion).

Statistical Analysis

We computed pooled odds ratio (OR) with 95% CIs under a random-effects model, employing the inverse variance and the restricted maximum likelihood methods.[17] *P* values were reported in their absolute, numeric form with 2 decimal places, and those <0.05 were considered statistically significant. Heterogeneity was assessed using the *Q* test and its *P* value, with the magnitude evaluated by I^2 values: 0% to 40% indicating low, 40% to 60% moderate, and >60% high heterogeneity.[10] We performed a leave-one-out sensitivity analysis under a random-effects model as needed to assess the impact of individual studies on the summary effect and heterogeneity. In addition, all main analyses were performed under a fixed-effect model to verify the robustness of the results across different statistical approaches. Version 2 of the Cochrane risk-of-bias tool for randomized trials was used to assess the risk of bias in the included studies.[18] We assessed publication bias using funnel plot analysis and Egger regression test. We prespecified a leave-one-out sensitivity analysis to assess the impact of studies with serious risk of bias, to be conducted if applicable. Statistical analysis and data visualization were performed using R 4.3.0 (R Core Team, 2023) with the *meta package* v.7.0-0.

RESULTS

Study Selection

A total of 1132 records were identified from MEDLINE (n=649), Embase (n=394), Cochrane (n=77), ClinicalTrials.gov (n=8), and additional records identified from the review of the included trial's references (n=4). After removing 220 duplicates, 912 records remained for title and abstract screening. Among these, 18 articles were selected for full-text evaluation. Ultimately, 8 RCTs met our inclusion criteria and were included in the present analysis (Figure 1).[7,12–16,19,20] The TIMELESS[9] and TWIST[21] (Tenecteplase in Wake-Up Ischemic Stroke Trial) trials were excluded as their design allowed MT, limiting their generalizability to populations without MT access. However, because mRS score of 0 to 1 outcome data for patients without MT was available in TWIST, we included results of this post hoc analysis in our meta-analysis, with the corresponding forest plot provided in Figure S1B.

Baseline Characteristics of the Included Studies and Patients

The included RCTs were multicentric and involved 263 centers from various countries, most of which were in Australia, China, Germany, Spain, and Japan. All studies ranged from 2014 to 2024; 3 trials[14–16] were phase II, whereas 5 trials[7,12,13,19,20] were phase III. Alteplase was the thrombolytic of choice in 5 trials,[12–14,19,20] and tenecteplase was used in 3.[7,15,16]

Among 1742 patients, 1107 (63.5%) were men, and 635 (36.5%) were women, with a mean age and SD of 69.8±9 years ranging from 62.7 to 79 years. The onset of stroke was reported by 5 articles,[7,12,13,15,19] from which 673 (50.1%) patients were unwitnessed, 378 (28.1%) patients had symptoms on awakening, and 292 (21.8%) had symptoms at a known time. Baseline mRS was reported as 0 to 1 in 1670 (96%) patients from 7 trials, whereas it was 0 to 2 in 69 (4%) patients from the EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial).[14] Thus, all patients included in this meta-analysis had a baseline mRS of ≤2. The median values of National Institutes of Health Stroke Scale scores ranged from 5 to 12. The median ischemic core volume ranged from 0.32 to 123.2 mL in 3 studies,[7,13,15] whereas the median Alberta Stroke Program Early CT Score was 9 in the 2 reporting trials.[13,16] The baseline characteristics of the included studies and patients are available in Table 1. Further details are available in Table S4.

Characteristics of the Selection and Intervention

The imaging criteria used for eligibility were DWI-FLAIR mismatch in the WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke),[19] THAWS (Thrombolysis for Acute Wake-Up and Unclear-Onset Strokes With Alteplase at 0.6 mg/kg),[13] and ROSE-TNK[15] (MRI-Guided Thrombolysis for Stroke Beyond Time Window by TNK) trials; magnetic resonance imaging or computed tomography perfusion imaging in the EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits),[12] TRACE-III,[7] and ECASS-4 (European Cooperative Acute Stroke Study-4) [20] trials; and no eligibility criteria based on perfusion imaging or DWI-FLAIR mismatch in the EXIT-BT (Extending the Time Window of Thrombolysis by Butyphthalide up to 6 Hours After Onset)[16] and EPITHET[14] trials. Further criteria details are described in Table 2.

Among the trials using alteplase as the intervention agent, EXTEND,[12] EPITHET,[14] ECASS-4,[20] and

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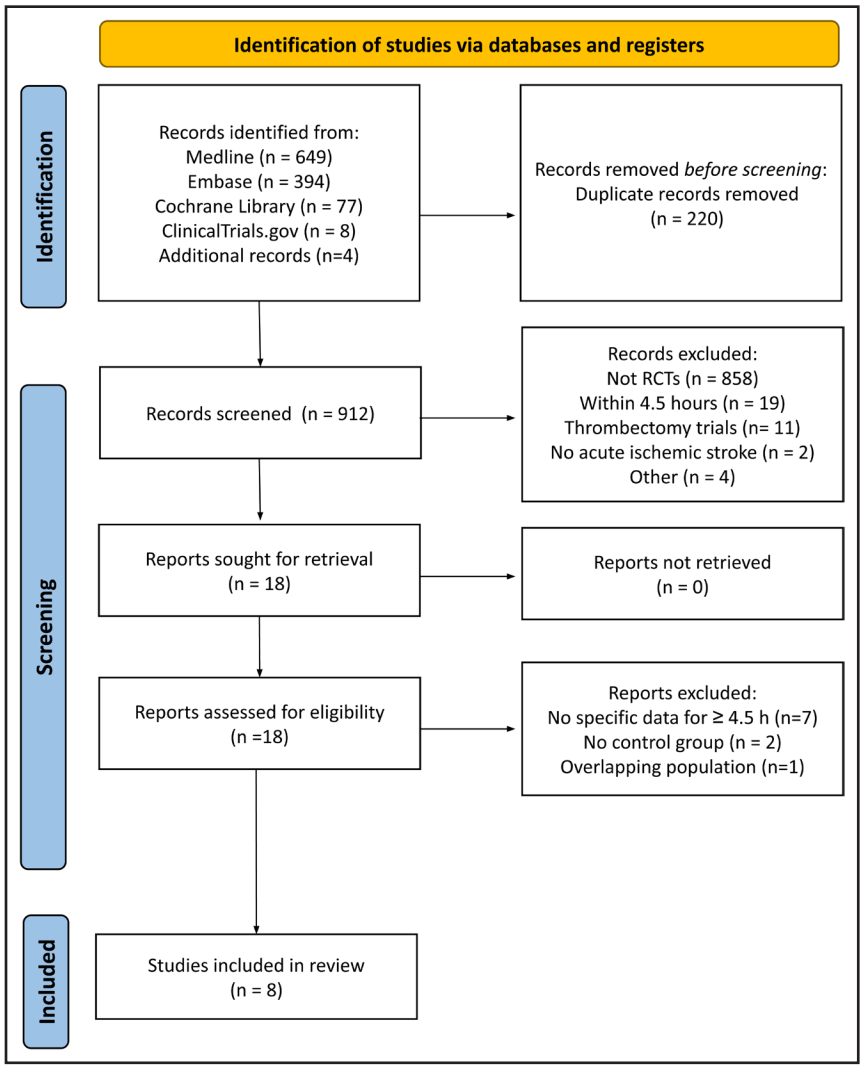

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.
RCT indicates randomized clinical trial.

WAKE-UP[19] trials administered a 0.9 mg/kg dose, whereas the THAWS[13] trial administered a 0.6 mg/kg dose. Tenecteplase was administered in a 0.25 mg/kg dose by the EXIT-BT,[16] ROSE-TNK,[15] and TRACE-III[7] trials. The control group was defined as general supportive care, including the use of antiplatelets, statins, and DI-3-n-butylphthalide 50 mg by EXIT-BT,[16] which combined DI-3-n-butylphthalide 50 mg with tenecteplase as the intervention. Furthermore, out of the 6 studies reporting a known treatment time window, 2[14,16] were from 4.5 to 6 hours, 2[12,20] were from 4.5 to 9, and 2[7,15] were from 4.5 to 24 hours. Two trials[13,19] primarily enrolled patients with wake-up stroke or unknown onset. To avoid including patients within the 4.5-hour window, we only included trials that stated the mean LKW to intervention was >4.5 hours, which was over 10 hours for these trials (Table 2).

The most common occlusion site was the M1 segment of the middle cerebral artery, with 391 (36.9%) patients, followed by the M2 segment of the middle cerebral artery, with 243 (22.9%) and internal carotid artery 236 (22.3%) patients. Other occlusion sites included the M3/M4 segments of the middle cerebral artery, anterior cerebral artery, posterior cerebral artery, and basilar artery. Three of the 8 trials did not report the occlusion site.[14,16,20] No MT was performed before randomization, and only 9 rescue procedures were allowed in the TRACE-III trial.[7] The median LKW to intervention time ranged from 5.5 to 12.8 hours. More detailed data for each therapy group are presented in Table 2.

Efficacy Outcomes

All studies reported excellent functional outcomes at 90 days, with a rate of 43.9% in the IVT group versus 36% in the control group (OR, 1.43 [95% CI, 1.17–1.75]; P=0.0005, Q=2.30; P=0.94; I^2=0%, number needed to treat=13). Good functional outcome at 90 days was 57.4% in the IVT group versus 50.5% in the control group (OR, 1.36 [95% CI, 1.12–1.66]; P=0.002; Q=2.07; P=0.96; I^2 0%).

Figure 2 demonstrates the ordinal distribution of mRS scores at 90 days across included trials.[7,12,13,15,16,19,20]

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Table 1. Baseline Characteristics of the Included Studies (n=8) and Patients

Study	Country (no. of centers)	Design (period)	Intervention	Sex (M/F)	Age	Onset of stroke	Baseline mRS	NIHSS score	Ischemic core volume, mL	ASPECT score
EXIT-BT 2024[16]	China (12)	Phase II open-label, blinded-end point RCT (2022)	Tenecteplase (50)	37/13	63.7±9.6	NA	0–1 (50)	5 (4–7)	NA	9 (8–10)
			Control (49)	28/21	64.8±10.25	NA	0–1 (49)	5 (4–6)	NA	9 (9–10)
EXTEND 2019[12]	Australia (16), New Zealand (1), Taiwan (10), Finland (1)	Phase III, placebo-controlled RCT (2010–2018)	Alteplase (113)	59/54	73.7±11.7	On awakening (73)	0–1 (113)	12 (8.0–17.0)	NA	NA
						NA (40)				
			Control (112)	66/46	71.0±12.7	On awakening (73)	0–1 (112)	10 (6.0–16.5)	NA	NA
						NA (39)				
EPITHET 2014[14]	Australia, New Zealand, Belgium, and United Kingdom (15)	Phase II, double-blind, placebo-controlled, RCT (2001–2007)	Alteplase (38)	23/15	75 (65–80)	NA	0–2 (38)	12 (7.0–18.0)	NA	NA
			Control (31)	19/12	73 (59–78)	NA	0–2 (31)	11 (8.0–17.0)	NA	NA
ECASS-4 2019[20]	Germany, Spain, Australia, Sweden, Italy, United Kingdom, and France (26)	Phase III, double-blind, placebo-controlled RCT (2014–2017)	Alteplase (61)	36/25	76 (65–83)	NA	0–1 (60)	10 (9)	NA	NA
			Control (58)	31/27	79 (67–84)	NA	0–1 (56)	9 (10)	NA	NA
WAKE-UP 2018[19]	Germany (23), Denmark (7), France (11), Spain (20), the Netherlands (1), Belgium (7), and Australia (1)	Phase III, double-blind, placebo-controlled RCT (2012–2017)	Alteplase (254)	165/89	65.3±11.2	Unwitnessed (254)	0–1 (254)	6 (4–9)	NA	NA
			Control (249)	160/89	65.2±11.9	Unwitnessed (249)	0–1 (249)	6 (4–9)	NA	NA
ROSE-TNK 2023[15]	China (14)	Phase II, blinded-end point RCT (2021–2022)	Tenecteplase (40)	31/9	62.68±8.87	On awakening (24)	0–1 (40)	7.5 (6–10.7)	0.32 (0–2.28)	NA
						NA (16)				
			Control (40)	26/14	62.80±8.56	On awakening (23)	0–1 (40)	7 (6–8.7)	0.4 (0.09–1.48)	NA
						NA (17)				
TRACE-III 2024[7]	China (58)	Phase III, open-label, blinded-end point RCT (2022–2023)	Tenecteplase (264)	183/81	67 (58–75)	Known onset time (143)	0 (230)	11 (7–15)	119.1 (79.8–177.2)	NA
						Unwitnessed (20)	1 (34)			
						On awakening (101)				
			Control (252)	167/85	68 (59–76)	Known onset time (149)	0 (216)	10 (7–14)	123.2 (74.6–180.1)	NA
						Unwitnessed (19)	1 (36)			
						On awakening (84)				
THAWS 2020[13]	Japan (40)	Phase III, open-label, blinded-end point RCT (2014–2018)	Alteplase (70)	45/25	73.2±12.4	Unwitnessed (70)	0–1 (70)	7 (4–13)	3.5 (0.8–14.2)	9 (8–10)
			Control (61)	31/30	75.8±11.9	Unwitnessed (61)	0–1 (61)	7 (5–12)	1.9 (0.3–11.1)	9 (8–10)

Data are presented as mean±SD, number (n), or median (interquartile range). ASPECTS indicates Alberta Stroke Program Early CT Score; ECASS-4, European Cooperative Acute Stroke Study-4; EPITHET, Echoplanar Imaging Thrombolytic Evaluation Trial; EXIT-BT, Extending the Time Window of Thrombolysis by Butyphthalide up to 6 Hours After Onset; EXTEND, Extending the Time for Thrombolysis in Emergency Neurological Deficits; F, female; M, male; NA, not available in the article; NIHSS, National Institutes of Health Stroke Scale; RCT, randomized clinical trial; ROSE-TNK, MRI-Guided Thrombolysis for Stroke Beyond Time Window by TNK; THAWS, Thrombolysis for Acute Wake-Up and Unclear-Onset Strokes With Alteplase at 0.6 mg/kg; TRACE-III, Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events-III; and WAKE-UP, Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke.

Other secondary efficacy outcomes and subgroup analysis results according to imaging criteria and thrombolytic agent are summarized in Table 3, and individual data reported by each trial can be found in Tables S2 and S3. All efficacy plots are available in Figures S1 through S5 and S13 through S17.

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Table 2. Characteristics of the Intervention

Study	Intervention	Imaging technique	Radiological eligibility criteria	Treatment time window*	Occlusion site	Endovascular thrombectomy	Last known well to intervention, h (median, IQR or mean±SD)
EXIT-BT 2024[16]	Tenecteplase 0.25 mg/kg† and NBP 50 mg daily (50)	NCCT or MRI	Confirmed acute ischemic stroke	4.5–6 h	NA	None	5.5 (5.2–5.7)
	Standard medical care and NBP 50 mg daily (49)‡			4.5–6 h	NA	None	5.5 (5.3–5.8)
EXTEND 2019[12]	Alteplase 0.9 mg/kg (113)§	MRI or perfusion CT	Perfusion lesion–ischemic core mismatch ratio ≥1.2, an absolute difference in volume >10 mL, and an ischemic core volume <70 mL	4.5–9 h	ICA (12)	None	7.2 (6.2–8.1)
					MCA M1 segment (44)		
					MCA M2 segment (25)		
					MCA M3/4 segments (23)		
					ACA (1)		
					PCA (6)		
					Other (2)		
	Placebo (112)			4.5–9 h	ICA (15)	None	7.5 (6.2–8.3)
					MCA M1 segment (38)		
					MCA M2 segment (31)		
					MCA M3/4 segments (18)		
					ACA (2)		
					PCA (4)		
					Other (4)		
EPITHET 2014[14]	Alteplase 0.9 mg/kg (38)§	NCCT, MRI perfusion‖	No eligibility criteria based on perfusion-diffusion MRI mismatch	4.5–6 h	NA	None	5.2 (5–5.7)
	Placebo (31)			4.5–6 h	NA	None	5.5 (5.2–5.8)
ECASS-4 2019[20]	Alteplase 0.9 mg/kg (61)§	MRI perfusion	Perfusion lesion–ischemic core mismatch ratio ≥1.2, an absolute difference in volume >10 mL, and an ischemic core volume <70 mL	4.5–9 h	NA	None	NA
	Placebo (58)			4.5–9 h	NA	None	NA
WAKE-UP 2018[19]	Alteplase 0.9 mg/kg (254)	MRI DWI-FLAIR mismatch	DWI with a high signal and visually normal FLAIR	≥4.5 h	ICA (24/249)	None	10.3 (8.1–12.0)
					MCA M1 segment (35/249)		
					MCA M2 segment (32/249)		
					Other (12/249)		
	Placebo (249)			≥4.5 h	ICA (11/246)	None	10.4 (8.1–12.1)
					MCA M1 segment (11/246)		
					MCA M2 segment (37/246)		
					Other (36/246)		
ROSE-TNK 2023[15]	Tenecteplase 0.25 mg/kg (40)†	MRI DWI/FLAIR mismatch	DWI with a high signal and visually normal FLAIR, DWI infarct volume <70 mL, DWI region ≤1/3 of MCA, 1/2 of the ACA, or 1/2 of PCA territories	4.5–24 h	Anterior circulation (24)	None	11.47±4.70
					Posterior circulation (16)		
	Standard medical care (40)‡			4.5–24 h	Anterior circulation (28)	None	12.52±4.68
					Posterior circulation (12)		

(*Continued*)

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Table 2. Continued

Study	Intervention	Imaging technique	Radiological eligibility criteria	Treatment time window*	Occlusion site	Endovascular thrombectomy	Last known well to intervention, h (median, IQR or mean±SD)
TRACE-III 2024[7]	Tenecteplase 0.25 mg/kg (264)†	MRI or CT perfusion	An ischemic core volume of <70 mL, a ratio of the volume of hypoperfused tissue to the ischemic core volume >1.8, and a difference in volume between the hypoperfused tissue and the ischemic core >15 mL	4.5–24 h	ICA (87) MCA M1 segment (119) MCA M2 segment (58)	None¶	12.4 (8.8–16.3)
	Standard medical care (252)‡			4.5–24 h	ICA (84) MCA M1 segment (130) MCA M2 segment (38)	None¶	12.8(9.0–17.5)
THAWS 2020[13]	Alteplase 0.6 mg/kg (70)§#	MRI DWI-FLAIR mismatch	DWI with a high signal and visually normal FLAIR	≥4.5 h	ICA (1) MCA M1 segment (6) MCA M2 segment (11) PCA (1)	None	10.2 (8.2–12.2)
	Standard medical care (61)‡			≥4.5 h	ICA (2) MCA M1 segment (8) MCA M2 segment (11) BA (1)	None	10.3 (7.7–11.8)

ACA indicates anterior cerebral artery; BA, basilar artery; CT, computed tomography; DWI, diffusion-weighted imaging; ECASS-4, European Cooperative Acute Stroke Study 4; EPITHET, Echoplanar Imaging Thrombolytic Evaluation Trial; EXIT-BT, Extending the Time Window of Thrombolysis by Butyphthalide up to 6 Hours After Onset; EXTEND, Extending the Time for Thrombolysis in Emergency Neurological Deficits; F, female; FLAIR, fluid-attenuated inversion recovery; ICA, internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NA, not available in the article; NBP, DI-3-n-butylphthalide; NCCT, noncontrast computed tomography; PCA, posterior cerebral artery; ROSE-TNK, MRI-Guided Thrombolysis for Stroke Beyond Time Window by TNK; THAWS, Thrombolysis for Acute Wake-Up and Unclear-Onset Strokes With Alteplase at 0.6 mg/kg; TRACE III, Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events–III; and WAKE-UP, Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke.

*Based on the time of symptom onset or last known well.

†Maximum dose of 25 mg.

‡Standard medical care was defined as antiplatelets, statins, blood pressure and glucose control, and general supportive care according to European or national guidelines for acute stroke.

§Maximum dose of 90 mg.

‖MRI perfusion was performed before the treatment but was not used to select patients. NCCT was performed to exclude acute hemorrhage and major early ischemic change.

¶None before randomization, rescue thrombectomy in 4 patients in the IVT group and 5 patients in the control group.

#Maximum dose of 60 mg.

Safety Outcomes

All studies except for EPITHET[14] reported the occurrence of sICH, with a rate of 2.7% in the IVT group versus 0.5% in the control group (OR, 4.25 [95% CI, 1.67–10.84]; P=0.002; Q=0.48; P=0.99; I^2=0%) and a 90-day all-cause mortality with 8.4% in the IVT group versus 6.5% in the control group (OR, 1.28 [95% CI, 0.87–1.89]; P=0.21; Q=4.63; P=0.59; I^2=0%). Secondary safety outcomes and subanalysis results according to

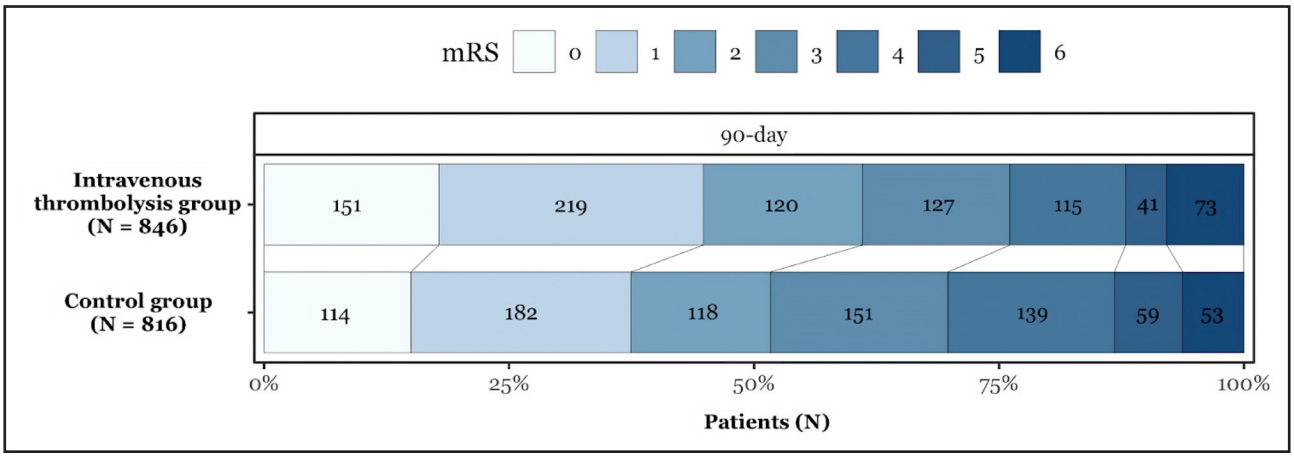

Figure 2. Ordinal modified Rankin Scale (mRS) distribution at 90 days.
Scores on the mRS range from 0 to 6: 0 indicates no symptoms, 1 indicates no clinically significant disability, 2 indicates slight disability, 3 indicates moderate disability, 4 indicates moderately severe disability, 5 indicates severe disability, and 6 indicates death.

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Table 3. Summary of the Pooled Statistical Findings

Outcomes	Odds ratios (95% CI), *P* value	I^2 (%)	*Q* statistic, *P* value	No. of studies	IVT vs control group; events/total
Overall					
Efficacy					
Primary outcomes					
mRS score 0–1 at 90 d	1.43 (1.17–1.75), 0.0005	0	2.30, *P*=0.94	8	385/877 vs 303/842
mRS score 0–2 at 90 d	1.36 (1.12–1.66), 0.002	0	2.07, *P*=0.96	8	508/885 vs 428/847
Secondary outcomes					
Ordinal mRS distribution at 90 d	NA	NA	NA	7	Displayed in Figure 2
Recanalization	2.65 (1.96–3.58), <0.0001	0	1.12, *P*=0.57	3	209/373 vs 122/368
Reperfusion	2.31 (1.62–3.29), <0.0001	0	1.76, *P*=0.42	3	123/383 vs 66/369
Early neurological improvement	2.70 (1.82–4.01), <0.0001	0	2.68, *P*=0.44	4	102/451 vs 45/450
Safety					
Primary outcomes					
sICH	4.25 (1.67–10.84), 0.002	0	0.48, *P*=0.99	7	23/848 vs 4/812
90-d all-cause mortality	1.28 (0.87–1.89), 0.21	0	4.63, *P*=0.96	7	71/848 vs 53/813
Secondary outcomes					
Any ICH	1.96 (1.06–3.63), 0.03	13	5.75, *P*=0.33	6	50/585 vs 23/561
Type II PH	5.14 (1.46–18.05), 0.01	0	0.69, *P*=0.88	4	16/608 vs 2/590
Systemic hemorrhage	3.10 (0.73–13.09), 0.12	0	0.37, *P*=0.54	6	8/792 vs 2/762
7-d all-cause mortality	1.11 (0.39–3.14), 0.84	0	0.07, *P*=0.78	2	8/173 vs 7/168
90-d intervention-related mortality	4.10 (0.67–25.04), 0.13	0	0.21, *P*=0.90	3	5/213 vs 0/208
DWI-FLAIR mismatch subanalysis					
Primary outcomes					
mRS score 0–1 at 90 d	1.34 (0.94–1.91), 0.11	0	1.90, *P*=0.39	3	184/354 vs 150/342
mRS score 0–2 at 90 d	1.28 (0.94–1.76), 0.12	0	0.98, *P*=0.61	3	249/362 vs 220/347
sICH	4.04 (0.67–24.19), 0.13	0	0.11, *P*=0.74	3	6/362 vs 1/344
90-d all-cause mortality	2.55 (0.91–7.09), 0.07	0	1.86, *P*=0.39	3	15/362 vs 5/344
MRI or CT perfusion subanalysis					
Primary outcomes					
mRS score 0–1 at 90 d	1.45 (1.08–1.94), 0.01	0	0.25, *P*=0.88	3	148/437 vs 110/420
mRS score 0–2 at 90 d	1.42 (1.08–1.87), 0.01	0	0.59, *P*=0.74	3	200/437 vs 157/420
sICH	4.54 (1.41–14.63), 0.01	0	0.31, *P*=0.85	3	16/437 vs 3/420
90-d all-cause mortality	1.14 (0.75–1.73), 0.54	0	0.71, *P*=0.70	3	55/437 vs 47/420
Alteplase subanalysis					
Primary outcomes					
mRS score 0–1 at 90 d	1.38 (1.08–1.78), 0.01	0	1.58, *P*=0.81	5	239/524 vs 190/501
mRS score 0–1 at 90 d–sensitivity analysis without THAWS[13]	1.46 (1.12–1.92), 0.005	0	0.32, *P*=0.96	4	207/456 vs 162/443
mRS score 0–2 at 90 d	1.27 (0.98–1.63), 0.07	0	1.09, *P*=0.90	5	326/532 vs 283/506
sICH	4.73 (1.35–16.63), 0.02	0	0.40, *P*=0.94	4	14/495 vs 2/472
90-d all-cause mortality	1.64 (0.90–2.99), 0.11	0	1.81, *P*=0.61	4	32/475 vs 19/472
Tenecteplase subanalysis					
Primary outcomes					
mRS score 0–1 at 90 d	1.47 (1.06–2.04), 0.02	0	0.47, *P*=0.79	3	146/353 vs 115/341
mRS score 0–2 at 90 d	1.51 (1.10–2.08), 0.01	0	0.23, *P*=0.89	3	182/353 vs 145/341
sICH	3.72 (0.91–15.13), 0.07	0	0.02, *P*=0.89	3	9/353 vs 2/340
90-d all-cause mortality	1.07 (0.65–1.76), 0.79	0	1.68, *P*=0.43	3	39/353 vs 34/341

CT indicates computed tomography; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; IVT, intravenous thrombolysis; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NA, not applicable; PH, parenchymal hemorrhage; sICH, symptomatic intracranial hypertension; and THAWS, Thrombolysis for Acute Wake-Up and Unclear-Onset Strokes With Alteplase at 0.6 mg/kg.

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imaging criteria and thrombolytic agent are summarized in Table 3, and individual data reported by each trial can be found in Tables S2 and S3. All the safety plots are available in Figures S6 through S17.

Quality Assessment

Overall, the risk of bias was judged to be low across the included studies (Figures S18 and S19). We found no evidence of publication bias in the funnel plot analysis and Egger regression test (Figures S20 and S21). However, analysis of funnel plots in the presence of <10 studies has limited accuracy.[10] Our results are also highlighted by no significant heterogeneity in the main and subgroup analyses (Table 3).

DISCUSSION

This meta-analysis of 8 RCTs across 263 centers presents a comprehensive evaluation of IVT with alteplase and tenecteplase versus standard medical care among patients with acute ischemic stroke presenting beyond the standard 4.5-hour window, without undergoing MT. The main finding of this meta-analysis is that compared with standard medical care, IVT significantly improves the rates of excellent and good functional outcomes at 90 days, although at the cost of a greater risk of sICH and a nonsignificant increase in 90-day mortality.

Our analysis consolidates the findings of individual trials and expands the understanding of IVT in the extended time window. The findings of this meta-analysis are consistent with earlier studies that demonstrated the efficacy of IVT within the standard 4.5-hour window.[22] This window extension is particularly noteworthy, as it challenges the traditional time-based criteria for IVT and proposes a paradigm shift supported by imaging biomarkers to assess tissue viability, which may be more relevant than time since stroke onset in determining the potential for recovery. Patients receiving IVT had a significantly higher rate of excellent recovery compared with the control group 43.9% versus 36%, respectively (OR, 1.43 [95% CI, 1.17–1.75]; *P*=0.0005), and good recovery (OR, 1.36 [95% CI, 1.12–1.66]; *P*=0.002), indicating a broad range of improved functional outcomes. Notably, this treatment effect mirrors the efficacy of IVT administered within the 4.5-hour window. An individual patient-level meta-analysis of 9 RCTs found an OR of 1.75 (95% CI, 1.35–2.27) within 3 hours and 1.26 (95% CI, 1.05–1.51) between 3 and 4.5 hours for the mRS score of 0 to 1 outcome.[23] Secondary efficacy outcomes, including significantly higher rates of recanalization, reperfusion, and early neurological improvement, further corroborate the beneficial effects of IVT.

Safety is a critical aspect of IVT. Our meta-analysis identified an increased risk of sICH associated with IVT, which is consistent with results from previous trials, including those limited to the 4.5-hour window.[6,22,23] The increased risk of sICH is an expected consequence of the thrombolytic mechanism, which promotes reperfusion but may also compromise vascular integrity. In addition, there was a numerical but not statistically significant increase in 90-day all-cause mortality in the IVT group. A slightly increased mortality is not unexpected, as a significant rise in early deaths has been reported in previous pooled analyses of trials,[6,23] which can at least partially be attributed to the increased rate of sICH. This underscores the need for careful patient selection and monitoring to mitigate risks while maximizing therapeutic benefits.

Advanced imaging techniques were crucial for patient selection, ensuring that only those with potentially salvageable brain tissue received IVT. DWI-FLAIR mismatch was used in WAKE-UP,[19] THAWS,[13] and ROSE-TNK[15] trials, offering a straightforward method for identifying eligible patients through visual assessment of magnetic resonance imaging sequences. In contrast, perfusion imaging, used in the EXTEND,[12] TRACE-III,[7] and ECASS-4[20] trials, involves image postprocessing but can identify patients with viable tissue even in the presence of marked hyperintensity on FLAIR. However, integrating automated software systems with perfusion imaging can effectively facilitate the detection of salvageable brain tissue and streamline patient selection.[7] Both DWI-FLAIR mismatch and perfusion imaging have been found to be effective in selecting patients who are expected to maximally benefit from IVT with unknown stroke onset.[6] Our subanalysis found that trials using perfusion imaging for patient selection had an OR of 1.45 (95% CI, 1.08–1.94; *P*=0.01) for excellent functional outcomes. For DWI-FLAIR mismatch, the OR was 1.34 (95% CI, 0.94–1.91; *P*=0.11). These results suggest that imaging criteria may influence the efficacy of IVT in the extended time window. Nonetheless, conclusive evidence regarding the validity of DWI-FLAIR mismatch is challenging because 2 trials employing DWI-FLAIR were terminated prematurely.[13,19] Of the 3 trials, only the WAKE-UP[19] trial, which included a large number of patients, found a significant benefit in achieving excellent functional outcomes at 90 days, while the ROSE-TNK[15] and THAWS[13] trials found no significant benefit. In addition, stroke severity at presentation was milder in these trials compared with those that used perfusion imaging, which may affect outcomes (Table 1).

Our subanalysis of trials using tenecteplase showed an OR of 1.47 (95% CI, 1.06–2.04; *P*=0.02) for excellent functional outcomes and an OR of 3.72 (95% CI, 0.91–15.13; *P*=0.07) for sICH. In trials using alteplase, the OR for excellent outcomes was 1.38 (95% CI, 1.08–1.78; *P*=0.01), with an OR of 4.73 (95% CI, 1.35–16.63; *P*=0.02) for sICH. Alteplase was administered at 0.9 mg/kg in most trials, except in THAWS[13] trial, which used 0.6 mg/kg. Tenecteplase was administered at 0.25 mg/kg. Our alteplase subanalysis results for excellent

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outcomes were in line but slightly different from the individual patient-level meta-analysis by Thomalla et al,[6] which included only partial data from the EXTEND and ECASS-4 trials and excluded the EPITHET trial. A sensitivity analysis excluding THAWS from the alteplase subanalysis revealed a numerically higher OR for excellent outcomes (OR, 1.46 [95% CI, 1.12–1.92]; *P*=0.005). These findings suggest that the thrombolytic agent and its dose may influence the safety and efficacy of IVT in the extended time window. However, patient selection criteria and sample sizes for IVT with alteplase and tenecteplase varied across the studies. Notably, of the 8 trials, 4 reported significant benefit,[7,12,14,19] 3 of which were larger,[7,12,19] with sample sizes from 225 to 516. In addition, the trials using tenecteplase were all conducted in China, which limits their generalizability. Furthermore, subgroup analyses were based on a small number of studies with limited statistical power. Recent evidence supports favorable outcomes with tenecteplase both within and beyond 4.5 hours,[7,24] and it appears to be cost-effective compared with alteplase in treating ischemic stroke.[25]

There are currently multiple ongoing trials investigating the use of IVT in the extended time window without MT (Table S5). The results of these trials may strengthen our understanding in the coming years. Future RCTs and patient-level meta-analyses may help identify ischemic stroke patient subgroups that could derive the most benefit from IVT with minimal risk in the extended window and clarify the role of imaging criteria in identifying these patients. By using imaging techniques to identify patients with salvageable brain tissue, clinicians can make more informed decisions for IVT, potentially improving outcomes for many patients who would otherwise be ineligible for IVT based on time criteria alone. The results of this meta-analysis also highlight the potential for extending IVT to broader patient populations. This includes those with unwitnessed strokes or strokes occurring during sleep, a common scenario where the exact onset time is unknown. From a patient and caregiver perspective, the findings of this meta-analysis offer hope for better recovery outcomes even in cases where stroke onset time is unknown or presentation is delayed.

This study has limitations. First, the inherent limitations of study-level meta-analysis precluded conducting subanalyses based on infarct size, occlusion site, and stroke severity at presentation. As a result, we were unable to determine whether the observed benefit of IVT was driven by patient subgroups, such as patients with proximal arterial occlusions or higher National Institutes of Health Stroke Scale scores. Second, most patients in the present meta-analysis were selected based on imaging rather than any ischemic stroke. As a result, minor nondisabling strokes were likely excluded, and disabling minor strokes were too few to draw conclusions. In addition, very severe strokes (eg, National Institutes of Health Stroke Scale >23, Alberta Stroke Program Early CT Score 0–5) were apparently not included either. This selection bias may have tilted the results in favor of IVT. Third, poststroke care was neither well-defined nor randomized, potentially influencing 90-day outcomes. The standard medical care varied across institutions, potentially affecting outcomes. In some trials, only a placebo was administered to the control group, or it was not specified if any standard medical care was provided. Last, variations in baseline characteristics, eligibility criteria (including stroke onset type, imaging selection and mismatch definitions, thrombolytic type, time from LKW), and end point definitions among the included trials are limitations of this meta-analysis due to the heterogeneity in these aspects.

Nevertheless, this is the largest systematic review of IVT use in patients with stroke beyond 4.5 hours, and none of the primary or secondary outcomes showed heterogeneity, which allowed us to carry out an ancillary fixed-effects analysis that, as expected, showed nearly identical results.[10] Despite the diverse range of centers worldwide and the varying publication years, homogenous findings further show the benefit of IVT in the extended time window. These results support further RCTs to optimize patient selection and replicate the TRACE-III trial outside of China, ideally with standardized imaging mismatch definitions and cutoff values, particularly in low-income countries where access to MT is limited.

CONCLUSIONS

Patients with ischemic stroke treated with IVT beyond the 4.5-hour window, without MT, had better functional outcomes compared with those receiving standard medical care. However, this benefit was accompanied by higher rates of sICH. The findings of this study are important for populations with limited access to MT. Further RCTs are necessary to optimize patient selection and maximize the benefits of IVT.

ARTICLE INFORMATION

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Dr Nguyen reports being Associate Editor of *Stroke*; part of the Advisory Board of Brainomix and Aruna Bio; and speaker for Genentech and Kaneka. Dr Jabbour is a consultant for Medtronic and Microvention. The other authors report no conflicts.

Supplemental Material

Tables S1–S5
Figures S1–S21

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